MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to novel benzazepine compounds, pharmaceutical compositions, processes for their preparation, and use thereof in treating muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M_1-M_5, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M_3 mAChRs mediate contractile responses (1989. The Muscarinic Receptors. The Humana Press, Inc., Clifton, NJ).

Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M_2 muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M_3 mAChRs. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M_3 mAChR-mediated hypermotility (Oprins, J. C. J., HP. Meijer, and J. A. Groot. 2000. Tumor Necrosis Factor-{alpha} Potentiates Ion Secretion Induced by Muscarinic Receptor Activation in the Human Intestinal Epithelial Cell Line HT29cl.19A. Ann NY Acad Sci 915:102-106). Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M_3 mAChRs. Thus the identification of subtytpe-selective mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

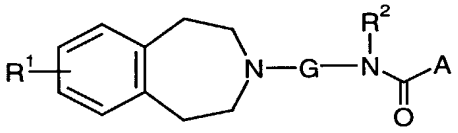
Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M_3 mAChRs. Conditions associated with an increase in stimulation of M_3 mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

SUMMARY OF THE INVENTION

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an mAChR and which method comprises administering an effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I).

The present invention also provides for the novel compounds of Formula (I), and pharmaceutical compositions comprising a compound of Formula (I), and a pharmaceutical carrier or diluent;



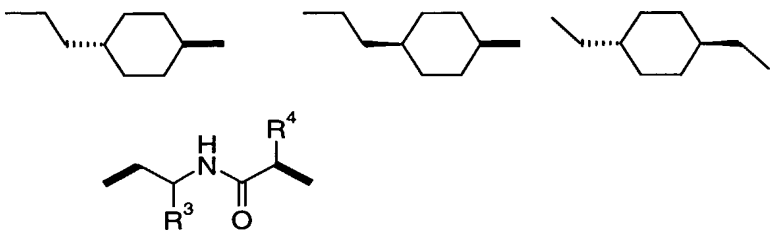
Formula (I)

wherein:

R^1 is selected from the group consisting of a substituent selected from: C_{1-6} alkanoyl, aroyl and aroylC_{1-6}alkyl, all optionally substituted;

R^2 is selected from the group consisting of a hydrogen atom or a C_{1-4}alkyl group;

G is selected from the group consisting of C_{4-7}alkyl or a group of the formula (a), (b), (c) or (d)

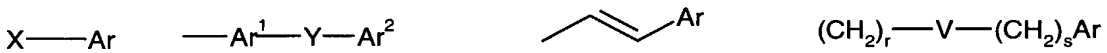


(a) (b) (c) (d)

Wherein,

R^3 and R^4 are, independently, selected from a group consisting of a hydrogen, C_{1-4}alkyl, aryl, or C_{1-2}alkylaryl;

A is selected from a group consisting of an optionally substituted C_{1-6}alkyl or a group of the formula (e), (f), (g) or (h):



(e) (f) (g) (h)

wherein

X is selected from a group consisting of a bond, NR^2, O or S;

Ar is selected from a group consisting of an optionally substituted phenyl ring or an optionally substituted 5- or 6- membered aromatic heterocyclic ring; or an optionally substituted bicyclic or heterobicyclic ring system;

Ar^1 and Ar^2 each independently is selected from a group consisting of an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered aromatic heterocyclic ring; and

Y is selected from a group consisting of a bond, -NHCO-, -CONH-, $-CH_2-$, or $-(CH_2)_mY^1(CH_2)_n-$, wherein Y^1 is selected from a group consisting of O, S, SO_2, or CO and m and n each represent zero or 1 such that the sum of m+n is zero or 1; provided that when A represents a group of formula (a), any substituent present in Ar *ortho* to the carboxamide moiety is necessarily a hydrogen or a methoxy group;

r and s are, independently, selected from a group consisting of an integer from zero to 3 such that the sum of r and s is equal to an integer from 1 to 6;

V is selected from a group consisting of a bond, O, S, -NHCO-, -CONH-, $CHNHCOR^3$;

and salts thereof.

In the compounds of formula (I) above an alkyl group or moiety may be straight or branched. Alkyl groups which may be employed include methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl and any branched isomers thereof such as isopropyl, t-butyl, sec-butyl, and the like.

When R^1 is selected from a group consisting of an aroyl, or aroylC_{1-4}alkyl, , the aryl moiety may be selected from an optionally substituted phenyl ring or an optionally substituted 5- or 6-membered heterocyclic ring. In the group R^1 an aryl moiety may be optionally substituted by one or more substituents selected from hydrogen, halogen, amino, cyano, C_{1-4}alkyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, C_{1-4}alkylamido, C_{1-4}alkanoyl, or R^5R^6NCO where each of R^5 and R^6 are, independently, selected from a group consisting of a hydrogen atom or C_{1-4}alkyl group.

An optionally substituted 5- or 6-membered heterocyclic aromatic ring, as defined for any of the groups Ar, Ar^1 or Ar^2 may contain from 1 to 4 heteroatoms selected from O, N or S. When the ring contains 2-4 heteroatoms, one is preferably selected from O, N and S and the remaining heteroatoms are preferably N. Examples of 5 and 6-membered heterocyclic groups include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, oxadiazolyl, thiadiazolyl, pyridyl, triazolyl, triazinyl, pyridazyl, pyrimidinyl, pyrazolyl, isothiazolyl, and isoxazolyl.

Examples of bicyclic, for example bicyclic aromatic or heteroaromatic, ring systems for Ar include naphthyl, indazolyl, indolyl, benzofuranyl, benzothienyl, benzothiazolyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinolinyl, quinoxolinyl, quinazolinyl, cinnolinyl, isoquinolinyl, pyrazolo[1,5-a]pyrimidyl, pyrrolo[3,2-b]pyridyl, pyrrolo[3,2-c]pyridyl, thieno[3,2-b]thiophenyl, 1,2-dihydro-2-oxo-quinolinyl, 3,4-dihydro-3-oxo-2*H*-benzoxazinyl, 1,2-dihydro-2-oxo-3*H*-indolyl.

The rings Ar, Ar^1, or Ar^2 may each independently be optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, or a hydroxy, oxo, cyano, nitro, trifluoromethyl, C_{1-4}alkyl, C_{1-4}alkoxy, C_{1-4}alkylenedioxy, C_{1-4}alkanoyl, C_{1-4}alkylsulfonyl, C_{1-4}alkylsulfinyl, C_{1-4}alkylthio, $R^7SO_2N(R^8)$-, $R^7R^8NSO_2$-, R^7R^8N-, R^7O_2C-, $R^7R^8NC(O)$-, or $R^7CON(R^8)$-group wherein each of R^7 and R^8 independently, selected from a group consisting

of a hydrogen atom or a C_{1-4} alkyl group, or R^7R^8 together form a C_{3-6} alkylene chain.

Alternatively, Ar and Ar^2 may be optionally substituted by one or more 5- or 6-membered heterocyclic rings, as defined above, optionally substituted by a C_{1-2} alkyl or R^7R^8N- group; wherein R^7 and R^8 are as defined above.

In the rings Ar and Ar^2 substituents positioned *ortho* to one another may be linked to form a 5- or 6- membered ring.

It will be appreciated that for use in medicine the salts of formula (I) should be physiologically acceptable. Suitable physiologically acceptable salts will be apparent to those skilled in the art and include for example acid addition salts formed with inorganic acids eg. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids eg. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Other non-physiologically acceptable salts eg. oxalates, may be used, for example in the isolation of compounds of formula (I) and are included within the scope of this invention. Also included within the scope of the invention are solvates and hydrates of compounds of formula (I).

Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

The compounds of formula (I) can exist in the form of *cis*- and *trans*-isomers with respect to the configuration at the cyclohexyl ring. When A represents a group (c) the compounds may also exist as geometric isomers around the double bond. The present invention includes within its scope all such isomers, including mixtures. Preferably the compounds of the invention are in the *trans* configuration with respect to the cyclohexyl ring. For compounds of formula (I) where A represents a group (c), *trans* geometry of the double bond is preferred.

In compounds of formula (I), it is preferred that R^1 represents a substituent selected from: a halogen atom, methyl, cyano, acetyl, trifluoromethyl, pentafluoroethyl, methylsulphonyl, methylsulphonyloxy or trifluoromethoxy group. Alternatively, it is preferred that R^1 represents a group Ar^3Z, where Z is a bond and Ar^3 is a 5- or 6-membered ring heterocycle, optionally substituted by a methyl

group, containing at least one N and one O atom. R^2 is preferably a hydrogen atom.

When the group A is a group of formula (a), preferred examples of Ar include optionally substituted phenyl, indolyl, pyrazolo[1,5-a]pyrimidyl, cinnolinyl, quinolinyl, benzo[b]furanyl or pyrrolopyridyl.

When the group A is a group of formula (b), preferred examples of Ar^1 include optionally substituted phenyl, Y is preferably a bond, and preferred examples of Ar^2 include optionally substituted phenyl, pyridyl, pyrimidinyl, isoxazolyl, oxazolyl or oxadiazolyl.

When the group A is a group of formula (c), preferred examples of Ar include optionally substituted phenyl.

It is also preferred that the rings Ar, Ar^1, or Ar^2 are each independently optionally substituted by one or more substituents selected from: a hydrogen or halogen atom, cyano, methoxy, trifluoromethyl, methylenedioxy, acetyl, acetylamino, methylsulfonyl, methylsulfonyloxy, methylaminosulfonyl, methylsulfonylamino, or methylaminocarbonyl group.

Certain of the substituted heteroaromatic ring systems included in compounds of formula (I) may exist in one or more tautomeric forms. The present invention includes within its scope all such tautomeric forms, including mixtures. The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C_{1-10}alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;

- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.
- "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C_{1-10} alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as also defined herein, unless otherwise indicated.

Particular compounds according to the invention include those specifically exemplified and named hereinafter, Most preferred:

2,8-dimethyl-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-5-quinolinecarboxamide;
2,8-Dimethyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-amide;
8-Methoxy-2-methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide;
8-Chloro-2-methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-5-quinoxalinecarboxamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2,2-diphenylacetamide;
2-Methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1H-indole-2-carboxamide;

1,1-dimethylethyl 2-{[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]carbonyl}benzoate;
8-chloro-2-methyl-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-5-quinolinecarboxamide;
2-methyl-8-(methyloxy)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-5-quinolinecarboxamide;
8-chloro-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-5-quinolinecarboxamide;

Preferred:

1,1-dimethylethyl ((1S)-2-[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]-2-oxo-1-{[(phenylmethyl)oxy]methyl}ethyl)carbamate formate;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-N'-(phenylmethyl)butanediamide;
N-{5-[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]-5-oxopentyl}benzamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-[(methylsulfonyl)amino]benzamide;
N^1-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-O-(phenylmethyl)-L-serinamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1-isoquinolinecarboxamide formate;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1,6-naphthyridine-2-carboxamide;
1,1-dimethylethyl ({3-[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]-3-oxopropyl}thio)acetate;
2-(dimethylamino)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)benzamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-3,3-diphenylpropanamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-(2-naphthalenyl)acetamide formate;

(2E)-3-(1H-imidazol-4-yl)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-propenamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-6-(1H-pyrrol-1-yl)-3-pyridinecarboxamide;
4-amino-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)butanamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-4-pyridinecarboxamide formate;
1,1-dimethylethyl {4-[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]-4-oxobutyl}carbamate;
3-[3,4-bis(methyloxy)phenyl]-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)propanamide;
N-{2-[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]-2-oxoethyl}-3-pyridinecarboxamide formate ;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1-phenylcyclopentanecarboxamide;
2-[4-(dimethylamino)phenyl]-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)acetamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1,8-naphthyridine-2-carboxamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-(4-pyridinyl)acetamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-4-oxo-4-phenyl-2-butenamide;
2-(5-hydroxy-1H-benzimidazol-1-yl)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)acetamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-pyrazinecarboxamide;
1-methyl-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1H-indole-2-carboxamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-(3-pyridinyl)-1,3-thiazole-4-carboxamide;
1,1-dimethylethyl {(1R)-2-[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]-2-oxo-1-phenylethyl}carbamate;

N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-3-pyridinecarboxamide 1-oxide formate;
3-(dimethylamino)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)benzamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1H-indole-2-carboxamide;
3-(1H-indol-3-yl)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)propanamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-quinolinecarboxamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-(1H-pyrrol-1-yl)benzamide;
1,1-dimethylethyl [(1R)-2-[(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)amino]-2-oxo-1-(3-pyridinylmethyl)ethyl]carbamate formate;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-1H-indole-3-carboxamide formate;
5-methyl-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-phenyl-2H-1,2,3-triazole-4-carboxamide;
N^3-[(4-methylphenyl)sulfonyl]-N^1-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-beta-alaninamide formate;
(2R)-2-amino-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-phenylethanamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-(2-pyrimidinylthio)acetamide formate;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-4-(1H-pyrrol-1-yl)benzamide;
N^1-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-3-(3-pyridinyl)-D-alaninamide;
(3E)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-4-phenyl-3-butenamide;
2-(1H-indol-3-yl)-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)acetamide;
N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)-2-[(phenylmethyl)thio]acetamide;

4-[4-(methyloxy)phenyl]-N-(trans-4-{2-[7-(2-methylpropanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]ethyl}cyclohexyl)butanamide;

2-Methyl-quinoline-5-carboxylic acid {4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-butyl}-amide;

2-Methyl-quinoline-5-carboxylic acid {8-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-octyl}-amide;

2-Methyl-quinoline-5-carboxylic acid [({4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-methyl]-amide;

(R)-1-[1-(2-Methyl-quinolin-5-yl)-methanoyl)-pyrrolidine-2-carboxylic acid {4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-amide2-Methyl-quinoline-5-carboxylic acid;

[2-({4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-ethyl]-amide;

2,8-Dimethyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-amide;

8-Methoxy-2-methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide;

8-Chloro-2-methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide;

2-Methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide;

N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-4-fluoro-benzamide;

N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(5-methyl-[1,2,4] oxadiazol-3-yl)-benzamide;

2-Methyl-quinoline-5-carboxylic acid {4-[2-(7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide;

1H-pyrrolo[2,3-*b*]pyridine-3-carboxylic acid -{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-amide;

(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(4-fluorophenyl)-acrylamide;

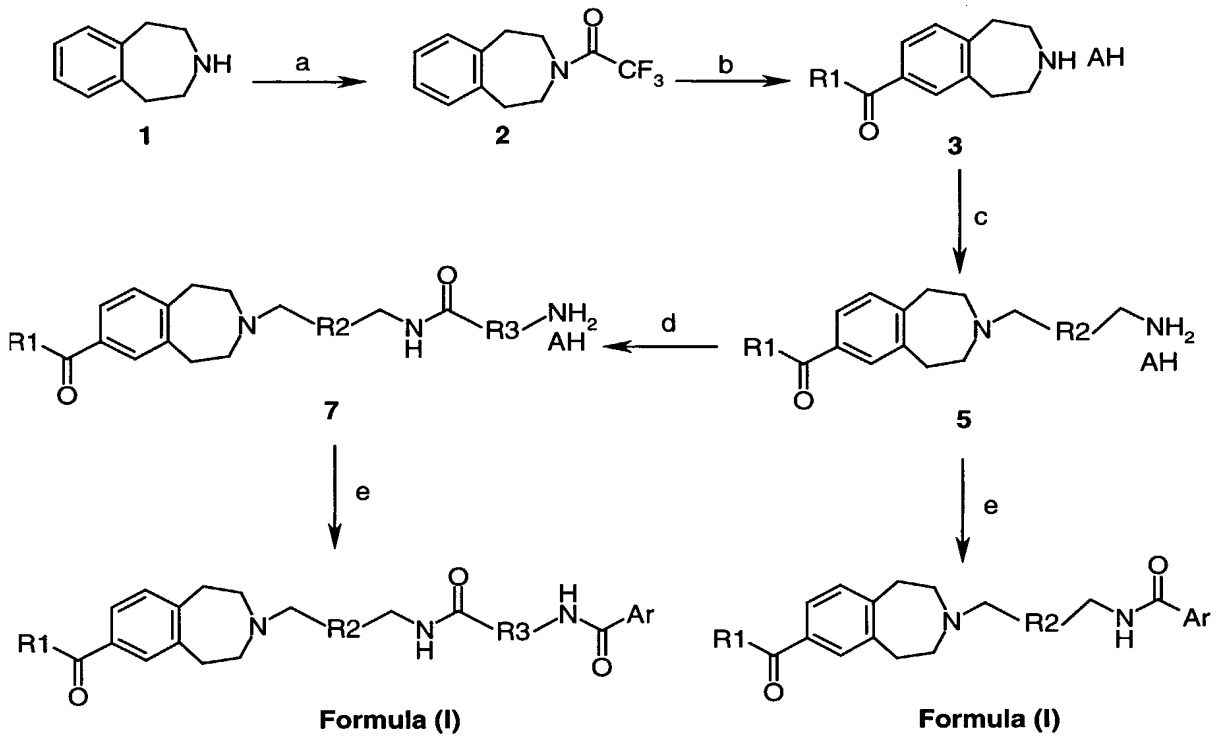
(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(3-methoxyphenyl)-acrylamide;

(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(2-cyanophenyl)-acrylamide;

(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(2-acetylphenyl)-acrylamide;
(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(3-thiophenyl)-acrylamide;
(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(8-(1,2-dihydro-2-oxo)-quinolinyl)-acrylamide;
(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(3-benzothiophenyl)-acrylamide;
(*E*)-N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-3-(3-benzothiophenyl)-acrylamide;
(*E*)-3-(4-Acetylamino-phenyl)-*N*-{4-[2-(7-acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-acrylamide;
N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-2-(2-aminobenzothiazol-6-yl)-acetamide;
4-Oxo-1,4-dihydro-quinoline-8-carboxylic acid-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-amide;
N-{4-[2-(7-Acetyl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-2-(benzo[*b*]thiophen-2-yl)-acetamide
and pharmaceutically acceptable salts thereof..

Methods of Preparation

The compounds of Formula (I) may be obtained by utilizing synthetic procedures, some of which are illustrated in the Schemes below. The synthesis provided for these Schemes is applicable for producing compounds of formula (I) with a variety of different R1, R2, R3, R' and R". While the Schemes are shown with compounds only of Formula (I), this is merely for illustration purpose only.



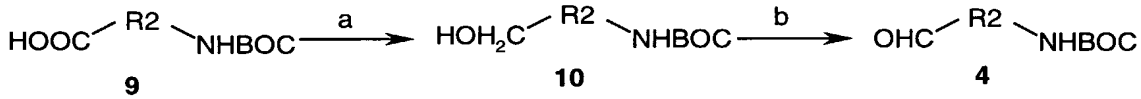
Reagents and conditions: a) TFAA, TEA; b) i) R_1-C(=O)-Cl , $AlCl_3$, CS_2; ii) 3N HCl, n-BuOH; c) i) $NaBH(OAc)_3$, OHC-R_2-NHBOC (**4**); ii) HCl, or TFA; d) i) BOCHN-R_3-COOH **6**, HOBT, EDC, DIEA; ii) HCl, or TFA; e) $ArCO_2H$ (**8**), HOBT, EDC, DIEA.

Scheme 1

The desired compounds of formula **(I)** can be prepared as outlined in Scheme 1. The 3H-3-benzazepine **1** was protected to yield trifluoroamide **2** using standard methods well know to those skilled in the art such as treatment with trifluoroacetic anhydride. The alkanoyl-3H-3-benzazepine **3** can be prepared from the corresponding **2** via Friedel-Crafts acylation followed by removal of the trifluoroacetyl group under acidic condition. The amine **5** can be prepared using the well known reductive amination reaction by treating the amines **3** with aldehydes **4** in the presence of a suitable reducing agent such as sodium triacetoxyborohydride. followed by removal of the protecting group using standard conditions well known in the art such as treatment with hydrochloric acid or trifluoroacetic acid. Compounds of Formula (I) can then be obtained by coupling of the amine **5** with a suitable carboxylic acid **8** in the presence of amide coupling reagents such as 1-hydroxybenzotriazole hydrate (HOBT) and 1-(3-dimethylaminopropyl)-3-

ethylcarbodiimide (EDC), or **5** be coupled with a suitable protected amino acid **6** gives the intermediate carbamate. This is subsequently deprotected under standard conditions such as treatment with hydrochloric acid or trifluoroacetic acid to yield the amine **7**. Finally, coupling of this amine with a suitable carboxylic acid **8** yields the target compound of formula (I). Alternatively, compounds **3** can be prepared according to Hadley *et al.* (WO 00/21951).

If the required N-protected alkyl aldehyde **4** is not commercially available, it can be prepared from a commercially available acid **9** as illustrated in Scheme 2. Thus, the acid **9** can be reduced to the corresponding alcohol **10** with boron trifluoride-THF complex. Oxidizing this alcohol **10** with pyridinium chlorochromate (PCC) produces the desired aldehyde **4**. In the case of R2= 1,4-trans-cyclohexyl, the compound **4** can be prepared according to Stemp *et al.* (*J. Med. Chem.* **2000**, *43*, 1878-85).

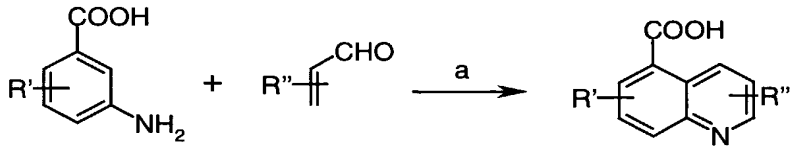


9 **10** **4**

Reagents and conditions: a) BH_3-THF; b) PCC or TPAP, NMO, 4ÅMs

Scheme 2

If the required acid **8** is of the quinoline-5-carboxylic acid-type, it can be prepared as outlined in Scheme 3. The 3-amino-benzolic acid **11** can be converted to quinoline-5-carboxylic acid **8** by condensing with a suitable propenal **12**. Otherwise, non-commercially available acids **8** can be prepared as described by Hadley *et al.* (WO 00/21951).



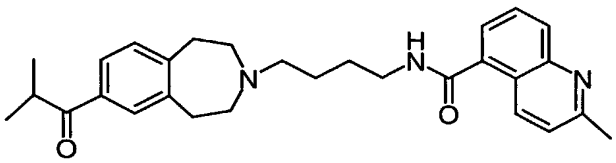
11 **12** **8**

Reagents and conditions: a) 9N HCl, ferrous sulfate, sodium 3-nitrobenzesulfonate

Scheme 3

SYNTHETIC EXAMPLES

Example 1



trans-2-Methyl-quinoline-5-carboxylic acid {4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-butyl}-amide:

1a) 2,2,2-Trifluoro-1-(1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethanone:
2,3,4,5-tetrahydro-1*H*-benzo[*d*] azepine (33.5g, 228 mmol) was dissolved in 93mL dichloromethane. Triethylamine (48mL, 342mmol) was added and the mixture was cooled on an icebath. TFAA (33.5 mL, 239mmol) was added dropwise from an addition funnel over 30 min. Stirring was contiuned overnight while the reaction mixture was allowed to warm to room temperature. The reaction mixture was washed with water, saturated aqueous $NaHCO_3$ and brine and the combined aqueous layers were extracted with 40 mL dichloromethane. The combined organic layers were dried over magnesium sulfate, filtered and concentrated *in vacuo* yielding 52.1 g of a pale yellow solid. LCMS: m/z 244 (M+H).

1b) 2-Methyl-1-[3-(2,2,2-trifluoro-ethanoyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-propan-1-one:
2,2,2-Trifluoro-1-(1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethanone (4.3g, 17.69 mmol) was dissolved in 20 mL carbondisulfide. Aluminum chloride (15.1g, 113 mmol) was added, followed by isobutyryl chloride (5.56mL, 53.07mmol) dropwise. The mixture was heated to 45°C for 1.5h and then at RT for 30min. The solvent was evaporated. The residue was dissolved in dichloromethane and cooled in an ice-bath. The extra aluminum chloride was quenched with 6N HCl. The mixture was washed with water (2X). The aquous layer was extracted with CH_2Cl_2 (2X) and the combined organic layers were washed with brine and dried over magesium sulfate. The solvent was removed *in vacuo*. The resulting crude was purified via column chromatography on silica gel using ethyl acetate / hexane (20/80, v/v) as mobile phase to give 4.74g of the title compound (85%). LCMS m/z 314 (M+H).

1c) 2-Methyl-1-(2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl)-propan-1-one:
2-Methyl-1-[3-(2,2,2-trifluoro-ethanoyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-propan-1-one (4.74g, 15.14 mmol) was dissolved in 84 mL 3N HCl and 50mL *n*-butanol. The mixture was heated to 100°C overnight, then additional 5h. After cooling to RT, the solvent was removed *in vacuo* and the crude hydrochloride was azeotroped off butanol with hexane, then treated with 1N NaOH and extracted with CH_2Cl_2 (4X). The combined organic layers were washed with brine and dried over magnesium sulfate. Removal of the solvent *in vacuo* to yield crude material which was used in the next step without further purification.

1d) 2-Methyl-quinoline-5-carboxylic acid:
To the stirring mixture of 3-aminobenzoic acid (10g, 72.52mmol), ferrous sulfate (5.74g, 20.66mmol) and sodium 3-nitrobenzene sulfonate (9.03g, 40.11mmol) in 150mL of 9N HCl at 90°C, was added crotonaldehyde (10.0mL, 121.5mmol) over 1.5h. After stirring for 22 h, the hot mixture was filtered and cooled to RT. The solid was precipitated out. The mixture was filtered. The solid was washed with acetone and collected to yield title product 7.009g. LCMS: m/z 188 (M+H).

1e) 2-Methyl-quinoline-5-carboxylic acid (4-hydroxy-butyl)-amide:
The mixture of 2-methyl-quinoline-5-carboxylic acid (250mg, 1.34mmol), 4-amino-1-butanol (120mg, 1.34mmol), EDC (260mg, 1.34mmol) and HOBT (18mg, 0.13mmol) in 10mL of $CHCl_3$ was stirred at RT for 1h. Triethylamine (0.72mL, 5.36mmol) was added. The resulting mixture was stirred overnight. After adding saturated $NaHCO_3$ and stirring for a while, the mixture was extracted with CH_2Cl_2 twice. The combined orgainc phase was washed with water and brine and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield the crude product 264mg which was used in the next step without further purification.

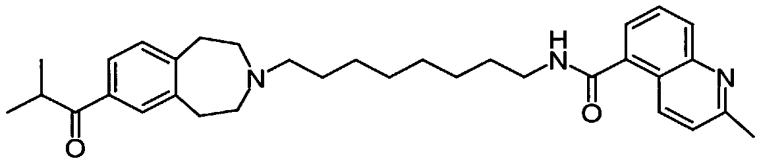
1f) 2-Methyl-quinoline-5-carboxylic acid (4-oxo-butyl)-amide:
To the suspension of the crude 2-methyl-quinoline-5-carboxylic acid (4-hydroxy-butyl)-amide (264mg, 1.02mmol) in 10mL of CH_2Cl_2 was added 4-methylmorpholine N-oxide (179mg, 1.53mmol), followed by TPAP (18mg, 0.051mmol) and 4Å molecular sieves (0.5g, 0.5g/mmol). The mixture was stirred at RT for 1.5h. The solvent was removed *in vacuo*. The residue was filtered through

silica pad, eluted with 100% EtOAc, followed by ethanol and dichloromethane (1:1, v/v) to give the crude material 186mg. This material was used in the next step without further purification.

1g) 2-Methyl-quinoline-5-carboxylic acid {4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-butyl}-amide:

To the mixture of crude 2-methyl-quinoline-5-carboxylic acid (4-oxo-butyl)-amide (93mg, 0.37mmol) and 2-methyl-1-(2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl)-propan-1-one (79mg, 0.36mmol) in 10mL of dichloroethane was added sodium triacetoxyborohydride (150mg, 0.73mmol). After stirring overnight, the mixture was quenched with water. The organic layer was isolated and concentrated to yield the crude product. Purification upon Gilson HPLC, eluting with acetonitrile/water/0.1% TFA (5/95, v/v to 60/40, v/v, over 10min), gave the desired product . LCMS: m/z 458 (M+H).

Example 2



trans-2-Methyl-quinoline-5-carboxylic acid {8-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-octyl}-amide

2a) {8-[7-(2-Methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-octyl}-carbamic acid *tert*-butyl ester:

To a solution of 2-methyl-1-(2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl)-propan-1-one (171mg, 0.79mmol) in 10mL of dichloroethane, (8-oxo-octyl)-carbamic acid *tert*-butyl ester (192mg, 0.79mmol) and sodium triacetoxyborohydride (219mg, 1.18mmol) were added. The mixture was stirred at RT overnight, followd by at 60°C for additional 4h. The mixture was cooled to RT, quenched with water and concentrated. The residue was dissolved in ethyl acetate, washed with water (3x) and brine, dried over magnesium sulfate and removed the solvent *in vacuo*. The resulting crude was purified via column chromatography on silica gel using

methanol:dichloromethane (5:95, v/v) as mobile phase to give 184mg (53%) of the title compound. LCMS m/z 445 (M+H).

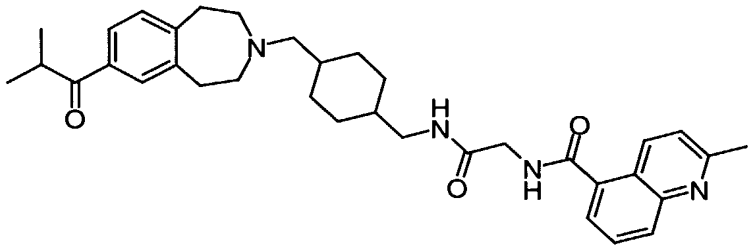
2b) 1-[3-(8-Amino-octyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-2-methyl-propan-1-one hydrochloride:

To a solution of {8-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-octyl}-carbamic acid *tert*-butyl ester (184mg, 0.42mmol) in 30mL of ethyl acetate, was bubbled in HCl gas for 5min. The mixture was then stirred at RT for 3h. Removed solvent *in vacuo* and pumped the residue to yield the crude product. This was used in the next step without further purition.

2c) 2-Methyl-quinoline-5-carboxylic acid {8-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-octyl}-amide:

To a solution of 1-[3-(8-amino-octyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-2-methyl-propan-1-one hydrochloride (184mg, 0.42mmol) in30mL of chloroform was added DIEA (361 μL, 2.1mmol), followed by 2-methyl-quinoline-5-carboxylic acid (116mg, 0.62mmol), EDC (79mg, 0.42mmol) and HOBT (6mg, 0.042mmol). The mixture was stirred at RT for 4h. The mixture was diluted with ethyl acetate, washed with water (2x) and brine, and dried over Na_2SO_4. The solvent was removed *in vacuo* to yield the crude product. Purification upon Gilson HPLC, eluting with acetonitrile/water/0.1% TFA (10/90, v/v to 50/50, v/v, over 10min), gave the desired product 48mg. LCMS: m/z 514 (M+H).

Example 3



trans-2-Methyl-quinoline-5-carboxylic acid [({4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-methyl]-amide

3a) {4-[7-(2-Methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester:
Following the general procedure described in Example 2a, 2-methyl-1-(2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl)-propan-1-one (294mg, 1.35mmol) and (4-formyl-cyclohexylmethyl)-carbamic acid *tert*-butyl ester (326mg, 1.35mmol) were reacted in the presence of sodium triacetoxyborohydride (429mg, 2.03mmol) to give the title compound 306mg. LCMS m/z 443 (M+H).

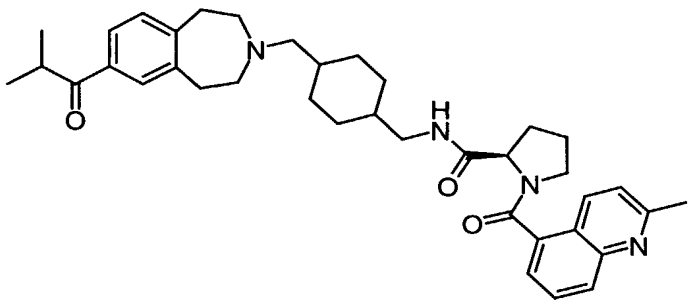
3b) 1-[3-(4-Aminomethyl-cyclohexylmethyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-2-methyl-propan-1-one:
Following the general procedure described in Example 2b, {4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamic acid *tert*-butyl ester (306mg, 0.69mmol) was bubbled HCl(g) to give the title compound 284mg. LCMS m/z 343 (M+H).

3c) [({4-[7-(2-Methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-methyl]-carbamic acid *tert*-butyl ester:
Following the general procedure described in Example 2c, 1-[3-(4-aminomethyl-cyclohexylmethyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-2-methyl-propan-1-one hydrochloride (95mg, 0.24mmol) was coupled with *tert*-butoxycarbonylamino-acetic acid (41mg, 0.24mmol) to give the crude product. This material was used in the next step without further purification. LCMS m/z 500 (M+H).

3d) 2-Methyl-quinoline-5-carboxylic acid [({4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-methyl]-amide:
To the solution of the crude [({4-[7-(2-Methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-methyl]-carbamic acid *tert*-butyl ester (0.24mmol) in 20mL of chloroform was added 0.11mL of TFA. The mixture was stirred at RT overnight. Additional 1mL of TFA was added to the mixture, and continued to stirred for another 6hr. The solvent was evaporated to give the crude 2-amino-N-{4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-acetamide. This material was coupled with 2-methyl-quinoline-5-carboxylic acid (48mg, 0.26mmol) by following the

general procedure described in Example 2c to give the title compound 72mg. LCMS m/z 569 (M+H).

.Example 4



trans- (R)-1-[1-(2-Methyl-quinolin-5-yl)-methanoyl)-pyrrolidine-2-carboxylic acid {4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-amide

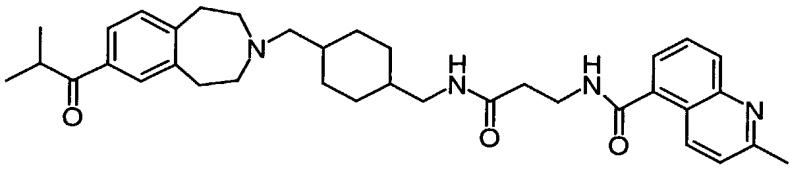
4a) (R)-2-({4-[7-(2-Methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester:

Following the general procedure described in Example 2c, 1-[3-(4-aminomethyl-cyclohexylmethyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-2-methyl-propan-1-one hydrochloride (95mg, 0.24mmol) was coupled with (R)-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (51mg, 0.24mmol) to give the crude product. This material was used in the next step without further purification. LCMS m/z 540 (M+H).

4b) (R)-1-[1-(2-Methyl-quinolin-5-yl)-methanoyl)-pyrrolidine-2-carboxylic acid {4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-amide:

Following the general procedure described in Example 3d, the crude (R)-2-({4-[7-(2-Methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester (0.24mmol) was stirred with 1.11mL of TFA to remove Boc. Then coupling with 2-methyl-quinoline-5-carboxylic acid (48mg, 0.26mmol) to give the title compound 65mg. LCMS m/z 609 (M+H).

Example 5

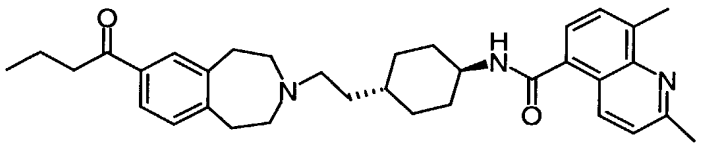


trans-2-Methyl-quinoline-5-carboxylic acid [2-({4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-ethyl]-amide:

5a) [2-({4-[7-(2-Methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-cyclohexylmethyl}-carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester:
Following the general procedure described in Example 2c, 1-[3-(4-aminomethyl-cyclohexylmethyl)-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl]-2-methyl-propan-1-one hydrochloride (95mg, 0.24mmol) was coupled with 3-*tert*-butoxycarbonylamino-propionic acid (45mg, 0.24mmol) to give the crude product. This material was used in the next step without further purification. LCMS m/z 514 (M+H).

5b) 2-Methyl-quinoline-5-carboxylic acid [2-({4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-ylmethyl]-cyclohexylmethyl}-carbamoyl)-ethyl]-amide
Following the general procedure described in Example 4d, the crude [2-({4-[7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl]-cyclohexyl-methyl}-carbamoyl)-ethyl]-carbamic acid *tert*-butyl ester (0.24mmol) was stirred with 1.11mL of TFA to remove the Boc protecting group. The resulting crude amine was then coupled with 2-methyl-quinoline-5-carboxylic acid (48mg, 0.26mmol) to give the title compound 68mg. LCMS m/z 583 (M+H).

Example 6



trans-2,8-Dimethyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-amide:

6a) 1-(7-Butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-2,2,2-trifluoro-ethanone:

2,2,2-trifluoro-1-(1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethanone (Example 1a) (1.41g, 5.80 mmol) ws dissolved in 7 mL carbondisulfide. Aluminum chloride (4.0g, 17.4 mmol) was added and the mixture was heated to 45°C. Butyryl chloride (1.8 mL, 17.4 mmol) was added dropwise over 15min. Stirring was continued at 45°C for 1h and then at RT for 1h. The reaction was quenched with 6N HCl, and diluted with water and ethyl acetate. The aquous layer was extracted with 2X100 mL EtOAc and the combined organic layers were washed with saturated aqueous sodium bicarbonate and brine and dried over magesium sulfate. The solvent was removed *in vacuo* and the crude material was recrystallized from EtOAc/hexanes to give 1.44g of an off-white solid. LCMS: m/z 314(M+H).

6b) 1-(2,3,4,5-Tetrahydro-1*H*-3H-3-benzazepin-7-yl)-butan-1-one:

1-(7-Butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-2,2,2-trifluoroethanone (1.44g, 4.60 mmol) was dissolved in 25 mL 3N HCl and 15 mL *n*-butanol. The mixture was heated to reflux for 6h. After cooling to RT the solvent was removed *in vacuo* and the crude hydrochloride was treated with 2N NaOH and extracted with 2X 100mL EtOAc. The combined organic layers were washed with brine and dried over magnesium sulfate. Removal of the solvent *in vacuo* and recrystallization from EtOAC/hexanes yielded 0.85g of a white solid. LCMS: m/z 218(M+H).

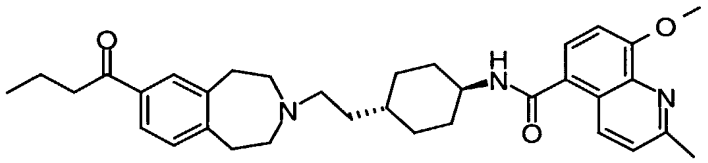
6c) 1-{3-[2-(4-Amino-cyclohexyl)-ethyl]-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl}-butan-1-one bistrifluoroacetate

To a solution of 1-(2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl)-butan-1-one (113mg, 0.47mmol) and [4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (102mg, 0.47mmol) in 5.8mL of dichloromethane, sodium triacetoxyborohydride (149mg, 0.71mmol) was added. The mixture was stirred at RT for 14h. The mixture was diluted with dichloromethane and washed with 10% aq. Na_2CO_3. The aqueous phase was extracted with dichloromethane (40mL). The combined organic phases was washed with brine, dried over magnesium sulfate and removed the solvent *in vacuo.* The resulting crude was disolved in the mixture of 10mL of dichloromethane and 4mL of trifluoroacetic acid. The resulting mixture was heated to 60°C for 1h, and then cooled to RT. The solvent was removed *in vacuo* to yield 230mg (86%) of the title compound: LCMS m/z 343 (M+H).

6d) 2,8-Dimethyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin-3-yl)-ethyl]-cyclohexyl}-amide:

The mixture of 1-{3-[2-(4-amino-cyclohexyl)-ethyl]-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl}-butan-1-one bistrifluoroacetate (58mg, 0.1mmol), 2,8-dimethyl-quinoline-5-carboxylic acid (51mg, 0.25mmol), EDC (48mg, 0.25mmol) and DIEA (44μL, 0.25mmol)in 1mL of CH_2Cl_2 was stirred at RT for 1h. The solvent was removed *in vacuo* to yield the crude product. Purification upon Gilson HPLC, eluting with acetonitrile/water/0.5% TFA (10/90, v/v to 90/10, v/v, over 10min), gave the desired product 6mg (9%). LCMS: m/z 526 (M+H).

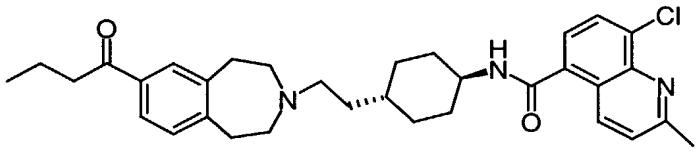
Example 7



trans-8-Methoxy-2-methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide:

Following the general procedure outlined in Example 6d, 1-{3-[2-(4-amino-cyclohexyl)-ethyl]-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl}-butan-1-one bistrifluoroacetate (58mg, 0.1mmol) coulped with 8-methoxy-2-methyl-quinoline-5-carboxylic acid (55mg, 0.25mmol) to yield the title compound 17mg (25%). LCMS m/z 542 (M+H).

Example 8

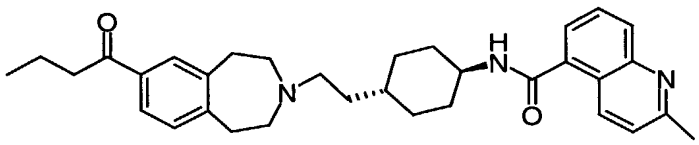


trans-8-Chloro-2-methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide:

Following the general procedure outlined in Example 6d, 1-{3-[2-(4-amino-cyclohexyl)-ethyl]-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl}-butan-1-one bistrifluoroacetate (58mg, 0.1mmol) coulped with 8-chloro-2-methyl-quinoline-5-

carboxylic acid (56mg, 0.25mmol) to yield the title compound 6mg (9%). LCMS m/z 546 (M+H).

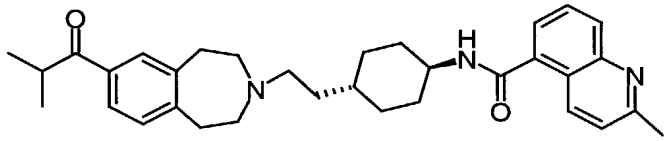
Example 9



trans-2-Methyl-quinoline-5-carboxylic acid {4-[2-(7-butyryl-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide:

Following the general procedure outlined in Example 6d, 1-{3-[2-(4-amino-cyclohexyl)-ethyl]-2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl}-butan-1-one bistrifluoroacetate (58mg, 0.1mmol) coulped with 2-methyl-quinoline-5-carboxylic acid (48mg, 0.25mmol) to yield the title compound 16mg (26%). LCMS m/z 512 (M+H).

Example 10



trans-2-Methyl-quinoline-5-carboxylic acid {4-[2-(7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide:

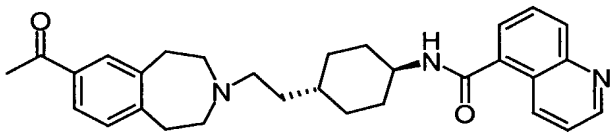
10a) 1-{3-[2-(4-Amino-cyclohexyl)-ethyl]-2,3,4,5-tetrahydro-1H-3H-3-benzazepin-7-yl}-2-methylpropan-1-one:

Following the general procedure of example 6c, 2-methyl-1-(2,3,4,5-tetrahydro-1*H*-3H-3-benzazepin-7-yl)-propan-1-one (2.7g, 12.4mmol) and [4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (3.0mg, 12.4mmol) in 120mL dichloroethane was treated with sodium triacetoxyborohydride (3.9g, 18.6mmol). The crude product (5.0g) was dissolved in 75 mL dichloromethane and TFA (7.5mL) was added. The mixture was stirred at room temperature for 2h after which the solvent was evaporated. The crude product was dissolved in a mixture of dichloromethane and ethyl acetate and washed with 2X100mL 10% aqueous sodium carbonate and brine. The aqueous layer was extracted with 2X100mL ethyl acetate and the combined organic layers were dried over magnesium sulfate.

Following filtration, the solvent was evaporated *in vacuo* to give 2.9g (68%) of the title compound. LCMS m/z 343 (M+H).

10b) *trans*-2-Methyl-quinoline-5-carboxylic acid {4-[2-(7-(2-methyl-propanoyl)-1,2,4,5-tetrahydro-3H-3-benzazepin3-yl)-ethyl]-cyclohexyl}-amide hydrochloride:
1-{3-[2-(4-Amino-cyclohexyl)-ethyl]-2,3,4,5-tetrahydro-1H-3H-3-benzazepin-7-yl}-2-methylpropan-1-one (275mg, 0.80 mmol) and 2-methyl-quinoline-5-carboxylic acid (197mg, 0.88mmol) was dissolved/suspended in 20mL chloroform. Diisopropylethylamine (1.0mL, 4.0 mmol), EDC hydrochloride (153mg, 0.80 mmol) and HOBt (11mg, 0.08 mmol) was added and the reaction mixture was stirred at room temp. for 14h. Dichloromethane was added and the mixture was washed with 2X 70 mL10% aqueous potassium carbonate, brine and dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the crude material was dissolved in dichloromethane. 4N HCl in dioxane (0.2ml, 0.8mmol) was added. Diethyl ether was added and the resulting precipitate was filtered and washed with diethyl ether yielding 320 mg of the title compound. LCMS m/z 512 (M+H)

Example 11



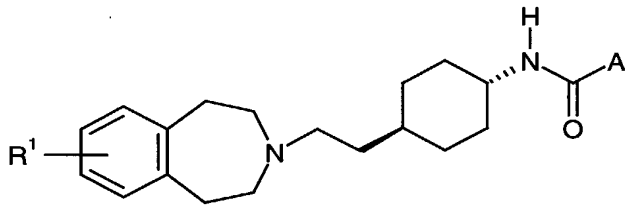
trans-7-Acetyl-3-(2-(1-(4-(5-quinolinyl)carboxamido)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine:

A mixture of 7-acetyl-*trans*-3-(2-(1-(4-amino)cyclohexyl)ethyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (0.105 g, 0.334 mmol) (prepared according to WO 00/21951), quinoline-5-carboxylic acid (0.064 g, 0.368 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.071 g, 0.368 mmol) and 1-hydroxybenzotriazole

hydrate (0.01 g, 0.065 mmol) in dichloromethane (6 ml) was shaken for 18 h. Saturated aqueous sodium hydrogen carbonate (6 ml) was added and shaking continued for a further 0.5 h. The organic layer was separated and pipetted onto a column of silica (10 g). Elution with 30 - 100% ethyl acetate - hexane gradient then 1 - 10% methanol - ethyl acetate gradient gave the title compound as a colorless solid (0.1 g, 64%). Mass spectrum (API+): 470 (MH^+);

Examples 12-81.

Examples 12-81 were prepared following the general procedure of example 11:



Example	R^1	A	Characterising Data: Mass Spectrum (API+)
12	7-COMe	-$CH_2C_6H_4$(4-F)	Mass: 451 (MH^+)
13	7-COMe	-C_6H_4(3-(3-(5-methyl)-1,2,4-oxadiazolyl))	Mass: 501 (MH^+)
14	7-COMe	3-pyrrolo[2,3-b]pyridyl	Mass: 459 (MH^+)
15	7-COMe	*trans*-CH=CHC_6H_4(4-F)	Mass: 463 (MH^+)
16	7-COMe	*trans*-CH=CHC_6H_4(3-OMe)	Mass: 475 (MH^+)
17	7-COMe	*trans*-CH=CHC_6H_4(2-CN)	Mass: 470 (MH^+)
18	7-COMe	*trans*-CH=CH(3-thiophenyl)	Mass: 451 (MH^+)
19	7-COMe	*trans*-CH=CH(8-(1,2-dihydro-2-oxo)-quinolinyl)	Mass: 512 (MH^+)
20	7-COMe	CH_2(3-benzothiophenyl)	Mass: 489 (MH^+)

21	7-COMe	*trans*-CH=CC$_6$H$_4$(4-NHCOMe)	Mass: 502 (MH$^+$)
22	7-COMe	-CH$_2$(6-(2-amino)-benzothiazolyl)	Mass: 505 (MH$^+$)
23	7-COMe	8-(1,4-dihydro-4-oxo)-quinolinyl	Mass: 486 (MH$^+$)
24	7-COMe	*trans*-CH=CHC$_6$H$_4$(2-COMe)	Mass: 487 (MH$^+$)
25	7-COMe	-CH$_2$(2-benzothiophenyl)	Mass: 489 (MH$^+$)
26	7-COCH(CH$_3$)$_2$	-(CH$_2$)$_3$NH$_2$	Mass: 428 (MH$^+$)
27	7-COCH(CH$_3$)$_2$	2-pyrazine	Mass: 449 (MH$^+$)
28	7-COCH(CH$_3$)$_2$	-CH$_2$(4-pyridinyl)	Mass: 462 (MH$^+$)
29	7-COCH(CH$_3$)$_2$	*trans*-CH=CH-(1H-imidazol-4-yl)	Mass: 463 (MH$^+$)
30	7-COCH(CH$_3$)$_2$	(*R*)-CH(NH$_2$)C$_6$H$_5$	Mass: 476 (MH$^+$)
31	7-COCH(CH$_3$)$_2$	2-indole	Mass: 486 (MH$^+$)
32	7-COCH(CH$_3$)$_2$	CH$_2$-CH=CH-C$_6$H$_5$	Mass: 487 (MH$^+$)
33	7-COCH(CH$_3$)$_2$	-C$_6$H$_4$(2-NMe$_2$)	Mass: 490 (MH$^+$)
34	7-COCH(CH$_3$)$_2$	-C$_6$H$_4$(3-NMe$_2$)	Mass: 490 (MH$^+$)
35	7-COCH(CH$_3$)$_2$	(*R*)-CH(NH$_2$)(3-pyridinyl)	Mass: 591 (MH$^+$)
36	7-COCH(CH$_3$)$_2$	4-pyridinyl	Mass: 448 (MH$^+$)
37	7-COCH(CH$_3$)$_2$	2-quinoline	Mass: 498 (MH$^+$)
38	7-COCH(CH$_3$)$_2$	5-quinoxaline	Mass: 499 (MH$^+$)
39	7-COCH(CH$_3$)$_2$	2-(1,8- naphthyridine	Mass: 499 (MH$^+$)

40	7-$COCH(CH_3)_2$	2-(1,6- naphthyridine	Mass: 499 (MH^+)
41	7-$COCH(CH_3)_2$	-CH_2(3-indole)	Mass: 500 (MH^+)
42	7-$COCH(CH_3)_2$	2-(1-methylindole)	Mass: 500 (MH^+)
43	7-$COCH(CH_3)_2$	-CH=CH-CO-C_6H_5	Mass: 501 (MH^+)
44	7-$COCH(CH_3)_2$	-$CH_2C_6H_4$(4-NMe_2)	Mass: 504 (MH^+)
45	7-$COCH(CH_3)_2$	-$CH_2SCH_2C_6H_5$	Mass: 507 (MH^+)
46	7-$COCH(CH_3)_2$	3-(pyridine oxide)	Mass: 464 (MH^+)
47	7-$COCH(CH_3)_2$	-C_6H_4(2-(1H-pyrrol-1-yl))	Mass: 512 (MH^+)
48	7-$COCH(CH_3)_2$	-C_6H_4(4-(1H-pyrrol-1-yl))	Mass: 512 (MH^+)
49	7-$COCH(CH_3)_2$	5-pyridinyl-(2-(1H-pyrrol-1-yl))	Mass: 513 (MH^+)
50	7-$COCH(CH_3)_2$	-$(CH_2)_2$-3-indole	Mass: 514 (MH^+)
51	7-$COCH(CH_3)_2$	1-phenyl cyclopentane-1-yl	Mass: 515 (MH^+)
52	7-$COCH(CH_3)_2$	-CH_2(1-(5-hydroxy)-1H-benzimidazol)	Mass: 517 (MH^+)
53	7-$COCH(CH_3)_2$	-$(CH_2)_2C_6H_4$(4-OMe)	Mass: 519 (MH^+)
54	7-$COCH(CH_3)_2$	-(*R*)-$CH(NH_2)CH_2OCH_2$ C_6H_5	Mass: 520 (MH^+)
55	7-$COCH(CH_3)_2$	-5-(2,8-dimethylquinoline)	Mass: 526 (MH^+)
56	7-$COCH(CH_3)_2$	-4-(5-methyl-2-phenyl-2H-1,2,3-triazole)	Mass: 528 (MH^+)
57	7-$COCH(CH_3)_2$	-$(CH_2)_3NHCO_2$-*t*-Bu	Mass: 528 (MH^+)
58	7-$COCH(CH_3)_2$	-4-(2-(3-pyridinyl)-1,3-thiazole)	Mass: 531 (MH^+)
59	7-$COCH(CH_3)_2$	3-indole	Mass: 486 (MH^+)

60	7-$COCH(CH_3)_2$	-$(CH_2)_2$-$CONHCH_2C_6H_5$	Mass: 532 (MH^+)
61	7-$COCH(CH_3)_2$	-5-(8-chloroquinoline)	Mass: 532 (MH^+)
62	7-$COCH(CH_3)_2$	-$(CH_2)_2$-C_6H_4-(3,4-dimethoxy)	Mass: 535 (MH^+)
63	7-$COCH(CH_3)_2$	-$CH(C_6H_5)_2$	Mass: 537 (MH^+)
64	7-$COCH(CH_3)_2$	-C_6H_4-(2-$NHSO_2Me$)	Mass: 540 (MH^+)
65	7-$COCH(CH_3)_2$	-CH_2-(2-pyrimidinyl)	Mass: 495 (MH^+)
66	7-$COCH(CH_3)_2$	-5-(2-methyl-8-methoxyquinoline)	Mass: 542 (MH^+)
67	7-$COCH(CH_3)_2$	1-isoquinoline	Mass: 498 (MH^+)
68	7-$COCH(CH_3)_2$	-$(CH_2)_2SCH_2CO_2$-*t*-Bu	Mass: 544 (M^+)
69	7-$COCH(CH_3)_2$	-$(CH_2)_4$-$NHCOC_6H_5$	Mass: 546 (MH^+)
70	7-$COCH(CH_3)_2$	-5-(2-methyl-8-chloroquinoline)	Mass: 546 (M^+)
71	7-$COCH(CH_3)_2$	-C_6H_4-(2-CO_2-*t*-Bu)	Mass: 547 (MH^+)
72	7-$COCH(CH_3)_2$	-CH_2-NHCO(3-pyridinyl)	Mass: 505 (MH^+)
73	7-$COCH(CH_3)_2$	-$CH_2CH(C_6H_5)_2$	Mass: 551 (MH^+)
74	7-$COCH(CH_3)_2$	-CH_2-(2-naphtyl)	Mass: 511 (MH^+)
75	7-$COCH(CH_3)_2$	(*R*)-$CH(NHCO_2$-*t*-Bu)C_6H_5	Mass: 576 (MH^+)
76	7-$COCH(CH_3)_2$	-$(CH_2)_2$-$NHSO_2$-C_6H_4(4-Me)	Mass: 568 (MH^+)
77	7-$COCH(CH_3)_2$	(*R*)-$CH(NHCO_2$-*t*-Bu)CH_2-(3-pyridinyl)	Mass: 591 (MH^+)
78	7-$COCH(CH_3)_2$	(*R*)-$CH(NHCO_2$-*t*-Bu)$CH_2OCH_2C_6H_5$	Mass: 620 (MH^+)

BIOLOGICAL EXAMPLES

The inhibitory effects of compounds at the mAChRs of the present invention are determined by the following *in vitro* and *in vivo* functional assays:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described (Sarau, H. M., R. S. Ames, J. Chambers, C. Ellis, N. Elshourbagy, J. J. Foley, D. B. Schmidt, R. M. Muccitelli, O. Jenkins, P. R. Murdock, N. C. Herrity, W. Halsey, G. Sathe, A. I. Muir, P. Nuthulaganti, G. M. Dytko, P. T. Buckley, S. Wilson, D. J. Bergsma, and D. W. Hay. 1999. Identification, molecular cloning, expression, and characterization of a cysteinyl leukotriene receptor. Mol Pharmacol 56:657-663). CHO cells stably expressing M_3 mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-acetoxymethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10 minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH_2PO_4, 25 mM NaH CO_3, 1.0 mM $CaCl_2$, 1.1 mM $MgCl_2$, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound ($1x10^{-11}$ – $1x10^{-5}$ M final in the assay) was added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels (Sullivan, E., E. M. Tucker, and I. L. Dale. 1999. Measurement of [Ca2+] using the Fluorometric Imaging Plate Reader (FLIPR). Methods Mol Biol 114:125-133). The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD

camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice (n = 6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in airway resistance that occur during bronchial challenge with methacholine (Hamelmann, E., J. SCHWARZE, K. TAKEDA, A. OSHIBA, G. á. LARSEN, C. á. IRVIN, and E. á. GELFAND. 1997. Noninvasive Measurement of Airway Responsiveness in Allergic Mice Using Barometric Plethysmography. Am.J.Respir.Crit.Care Med. 156:766-775). Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally, i.v., i.p. or p.o, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

The present compounds are useful for treating a variety of indications, including but not limited to respiratory-tract disorders such as chronic obstructive lung disease, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, and allergic rhinitis; gastrointestinal-tract disorders such as irritable bowel syndrome, spasmodic colitis, gastroduodenal ulcers, gastrointestinal convulsions or hyperanakinesia, diverticulitis, pain accompanying spasms of gastrointestinal smooth musculature; urinary-tract disorders accompanying micturition disorders including neurogenic pollakisuria, neurogenic bladder, nocturnal enuresis, psychosomatic bladder, incontinence associated with bladder spasms or chronic cystitis, urinary urgency or pollakiuria, and motion sickness.

Methods of administering the present compounds will be readily apparent to the skilled artisan.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or

blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Formulations generally contain a powder mix for inhalation of the compound of the invention and a suitable powder base (carrier substance) such as lactose or starch. Use of lactose is preferred. Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients.

Suitably, the medicament dispenser is of a type selected from the group consisting of a reservoir dry powder inhaler (RDPI), a multi-dose dry powder inhaler (MDPI), and a metered dose inhaler (MDI).

By reservoir dry powder inhaler (RDPI) it is meant an inhaler having a reservoir form pack suitable for comprising multiple (un-metered doses) of medicament in dry powder form and including means for metering medicament dose from the reservoir to a delivery position. The metering means may for example comprise a metering cup, which is movable from a first position where the cup may be filled with medicament from the reservoir to a second position where the metered medicament dose is made available to the patient for inhalation.

By multi-dose dry powder inhaler (MDPI) is meant an inhaler suitable for dispensing medicament in dry powder form, wherein the medicament is comprised within a multi-dose pack containing (or otherwise carrying) multiple, define doses (or parts thereof) of medicament. In a preferred aspect, the carrier has a blister pack form, but it could also, for example, comprise a capsule-based pack form or a carrier onto which medicament has been applied by any suitable process including printing, painting and vacuum occlusion.

The formulation can be pre-metered (eg as in Diskus, see GB 2242134 or Diskhaler, see GB 2178965, 2129691 and 2169265) or metered in use (eg as in Turbuhaler, see EP 69715). An example of a unit-dose device is Rotahaler (see GB 2064336). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also,

preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

In one aspect, the multi-dose pack is a blister pack comprising multiple blisters for containment of medicament in dry powder form. The blisters are typically arranged in regular fashion for ease of release of medicament therefrom.

In one aspect, the multi-dose blister pack comprises plural blisters arranged in generally circular fashion on a disc-form blister pack. In another aspect, the multi-dose blister pack is elongate in form, for example comprising a strip or a tape.

Preferably, the multi-dose blister pack is defined between two members peelably secured to one another. US Patents Nos. 5,860,419, 5,873,360 and 5,590,645 describe medicament packs of this general type. In this aspect, the device is usually provided with an opening station comprising peeling means for peeling the members apart to access each medicament dose. Suitably, the device is adapted for use where the peelable members are elongate sheets which define a plurality of medicament containers spaced along the length thereof, the device being provided with indexing means for indexing each container in turn. More preferably, the device is adapted for use where one of the sheets is a base sheet having a plurality of pockets therein, and the other of the sheets is a lid sheet, each pocket and the adjacent part of the lid sheet defining a respective one of the containers, the device comprising driving means for pulling the lid sheet and base sheet apart at the opening station.

By metered dose inhaler (MDI) it is meant a medicament dispenser suitable for dispensing medicament in aerosol form, wherein the medicament is comprised in an aerosol container suitable for containing a propellant-based aerosol medicament formulation. The aerosol container is typically provided with a metering valve, for example a slide valve, for release of the aerosol form medicament formulation to the patient. The aerosol container is generally designed to deliver a predetermined dose of medicament upon each actuation by means of the valve, which can be opened either by depressing the valve while the container is held stationary or by depressing the container while the valve is held stationary.

Where the medicament container is an aerosol container, the valve typically comprises a valve body having an inlet port through which a medicament aerosol formulation may enter said valve body, an outlet port through which the aerosol

may exit the valve body and an open/close mechanism by means of which flow through said outlet port is controllable.

The valve may be a slide valve wherein the open/close mechanism comprises a sealing ring and receivable by the sealing ring a valve stem having a dispensing passage, the valve stem being slidably movable within the ring from a valve-closed to a valve-open position in which the interior of the valve body is in communication with the exterior of the valve body via the dispensing passage.

Typically, the valve is a metering valve. The metering volumes are typically from 10 to 100 µl, such as 25 µl, 50 µl or 63 µl. Suitably, the valve body defines a metering chamber for metering an amount of medicament formulation and an open/close mechanism by means of which the flow through the inlet port to the metering chamber is controllable. Preferably, the valve body has a sampling chamber in communication with the metering chamber via a second inlet port, said inlet port being controllable by means of an open/close mechanism thereby regulating the flow of medicament formulation into the metering chamber.

The valve may also comprise a 'free flow aerosol valve' having a chamber and a valve stem extending into the chamber and movable relative to the chamber between dispensing and non-dispensing positions. The valve stem has a configuration and the chamber has an internal configuration such that a metered volume is defined therebetween and such that during movement between is non-dispensing and dispensing positions the valve stem sequentially: (i) allows free flow of aerosol formulation into the chamber, (ii) defines a closed metered volume for pressurized aerosol formulation between the external surface of the valve stem and internal surface of the chamber, and (iii) moves with the closed metered volume within the chamber without decreasing the volume of the closed metered volume until the metered volume communicates with an outlet passage thereby allowing dispensing of the metered volume of pressurized aerosol formulation. A valve of this type is described in U.S. Patent No. 5,772,085. Additionally, intra-nasal delivery of the present compounds is effective.

To formulate an effective pharmaceutical nasal composition, the medicament must be delivered readily to all portions of the nasal cavities (the target tissues) where it performs its pharmacological function. Additionally, the medicament should remain in contact with the target tissues for relatively long periods of time. The longer the medicament remains in contact with the target tissues, the medicament must be capable of resisting those forces in the nasal passages that function to remove

particles from the nose. Such forces, referred to as 'mucociliary clearance', are recognised as being extremely effective in removing particles from the nose in a rapid manner, for example, within 10-30 minutes from the time the particles enter the nose.

Other desired characteristics of a nasal composition are that it must not contain ingredients which cause the user discomfort, that it has satisfactory stability and shelf-life properties, and that it does not include constituents that are considered to be detrimental to the environment, for example ozone depletors.

A suitable dosing regime for the formulation of the present invention when administered to the nose would be for the patient to inhale deeply subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is manually compressed. This procedure would then be repeated for the other nostril.

A preferable means for applying the formulation of the present invention to the nasal passages is by use of a pre-compression pump. Most preferably, the pre-compression pump will be a VP7 model manufactured by Valois SA. Such a pump is beneficial as it will ensure that the formulation is not released until a sufficient force has been applied, otherwise smaller doses may be applied. Another advantage of the pre-compression pump is that atomisation of the spray is ensured as it will not release the formulation until the threshold pressure for effectively atomising the spray has been achieved. Typically, the VP7 model may be used with a bottle capable of holding 10-50ml of a formulation. Each spray will typically deliver 50-100µl of such a formulation, therefore, the VP7 model is capable of providing at least 100 metered doses.

Examples of Nasal Formulations

Example 1 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

	to 100%
Active	0.1% w/w
Polysorbate 80	0.025% w/w
Avicel RC591	1.5% w/w
Dextrose	5.0% w/w

BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation. The device was fitted into a nasal actuator (Valois).

Example 2 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

Active	0.005% w/w
Tyloxapol	2% w/w
dextrose	5% w/w
BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle (plastic or glass) fitted with a metering valve adapted to dispense 50 or 100 µl per actuation

The device was fitted into a nasal actuator (Valois, e.g. VP3, VP7 or VP7D)

Example 3 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

active	0.05% w/w
Triton X-100	5% w/w
Dextrose	4% w/w
BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation.

Example 4 : Nasal formulation containing active

A formulation for intranasal delivery was prepared with ingredients as follows:

active	0.05% w/w
Tyloxapol	5% w/w

dextrose	5% w/w
BKC	0.015% w/w
EDTA	0.015% w/w
water	to 100%

in a total amount suitable for 120 actuations and the formulation was filled into a bottle fitted with a metering valve adapted to dispense 50 or 100 µl per actuation The device was fitted into a nasal actuator (Valois).

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.